

PATENT
Customer Service No. 22,852
Attorney Docket No. 4185.0005-09

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
David F. CARMICHAEL *et al.*)
(Divisional of U.S. Application No. 09/452,817))
Serial No.: Not Yet Assigned) Group Art Unit: Not Yet Assigned
Filed: November 14, 2001) Examiner: Not Yet Assigned
For: HUMAN COLLAGENASE INHIBITOR,)
RECOMBINANT VECTOR SYSTEM)
FOR USING SAME AND)
RECOMBINANT DNA METHOD FOR)
THE MANUFACTURE OF SAME (As)
Amended))

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to the examination of the above application, please amend this application
as follows:

IN THE TITLE OF THE APPLICATION:

Please delete the title of the application and insert:

--Human Collagenase Inhibitor, Recombinant Vector System for Using Same

And Recombinant DNA Method for the Manufacture of Same.--

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005
202-408-4000

IN THE SPECIFICATION:

Please replace the paragraph on page 4, beginning at line 4, with the following paragraph:

--Surprisingly, the present inventors have discovered a portable DNA sequence capable of directing the recombinant-DNA synthesis of metalloproteinase inhibitors. These metalloproteinase inhibitors are biologically equivalent to those isolated from human skin fibroblast cultures. The metalloproteinase inhibitors of the present invention, prepared by the recombinant DNA methods set forth herein, will enable increased research into prevention and treatment of metalloproteinase-induced connective tissue diseases. In addition, the metalloproteinase inhibitors of the present invention are useful in neutralizing metalloproteinases, including the excess metalloproteinase associated with disease states. Therefore, it is believed that a cure for these diseases will be developed which will embody, as an active ingredient, the metalloproteinase inhibitors of the present invention. Furthermore, the metalloproteinase inhibitors of the present invention are capable of interacting with their metalloproteinase targets in a manner which allows the development of diagnostic tests for degradative connective tissue diseases using the newly discovered inhibitors.--

Please replace the paragraph on page 7, beginning at line 11, with the following paragraph:

--The coding strand of a first preferred DNA sequence which has been discovered has the following nucleotide sequence (SEQ ID No: 5):--

Please replace the paragraph on page 8, beginning at line 12, with the following paragraph:

--A second preferred DNA sequence has been discovered which has an additional nucleotide sequence 5' to the initiator sequence. This sequence, which contains as the eighty-second through four-hundred-thirty-second nucleotides nucleotides 1 through 351 of the first preferred sequence set forth above, has the following nucleotide sequence (SEQ ID No: 6):--

Please replace the paragraph on page 9, beginning at line 5, with the following paragraph:

--A third preferred DNA sequence which incorporates the 5' region of the second preferred sequence and the 3' sequence of the first preferred sequence, has the following nucleotide sequence (SEQ ID No: 7):--

Please replace the last paragraph on page 13 with the following paragraph:
--A first preferred portable DNA sequence of the present invention has a nucleotide sequence SEQ ID No: 5 as follows:--

Please insert, on page 15, after line 5, "Thymidylic Acid T," the following new paragraphs:

--The first preferred portable DNA sequence encodes a metalloproteinase inhibitor having, as a mature protein, the amino acid sequence SEQ ID No: 1 of Table 1 (using the three letter abbreviations for amino acids). The amino acid at position +1 is cysteine (Cys). The amino acid at position +184 is alanine (Ala). As seen in the other preferred portable DNA sequences described below, the DNA sequence encoding a metalloproteinase inhibitor may also encode leader sequences. The leader sequences may be designated by negative numbers beginning with -1.

TABLE 1

	+1	
Cys Thr Cys Val Pro Pro His Pro Gln	9	
Thr Ala Phe Cys Asn Ser Asp Leu Val Ile Arg Ala Lys Phe Val Gly Thr Pro Glu Val	29	
Asn Gln Thr Thr Leu Tyr Gln Arg Tyr Glu Ile Lys Met Thr Lys Met Tyr Lys Gly Phe	49	
Gln Ala Leu Gly Asp Ala Ala Asp Ile Arg Phe Val Tyr Thr Pro Ala Met Glu Ser Val	69	
Cys Gly Tyr Phe His Arg Ser His Asn Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu	89	
Gln Asp Gly Leu Leu His Ile Thr Thr Cys Ser Phe Val Ala Pro Trp Asn Ser Leu Ser	109	
Leu Ala Gln Arg Arg Gly Phe Thr Lys Thr Tyr Thr Val Gly Cys Glu Glu Cys Thr Val	129	
Phe Pro Cys Leu Ser Ile Pro Cys Lys Leu Gln Ser Gly Thr His Cys Leu Trp Thr Asp	149	
Gln Leu Leu Gln Gly Ser Glu Lys Gly Phe Gln Ser Arg His Leu Ala Cys Leu Pro Arg	169	
Glu Pro Gly Leu Cys Thr Trp Gln Ser Leu Arg Ser Gln Ile Ala		

+184 SEQ ID NO: 1--

Please replace the paragraph on page 15, beginning at line 6 in the original specification, with the following paragraph:

--A second preferred portable DNA sequence of the present invention has the following nucleotide sequence (SEQ ID No: 6):--

Please replace the final paragraph on page 15, bridging to page 16, line 2, with the following paragraph:

--In this second preferred sequence, an open reading frame exists from nucleotides 1 through 432. The first methionine of this reading frame is encoded by nucleotides by 49 through 51 and is the site of translation initiation. It should be noted that the amino acid sequence prescribed by nucleotides 49 through 114 is not found in the mature metalloproteinase. It is believed that this sequence is the leader peptide of the human protein.--

Please replace the paragraph on page 16, beginning at line 3, with the following paragraph:

--A third preferred portable DNA sequence has the nucleotide sequence (SEQ ID No: 7):--

Please replace the nucleotide sequence on page 28, beginning on line 14, with the following nucleotide sequence:

HgiAI
--(SEQ ID No: 8) 5' GAT CCG TGC ACT TGT GTT CCA CCA CAC
(SEQ ID No: 9) GC ACG TGA ACA CAA GGT GGT GTG
CCA CAA ACT GCT TTC TGT AAC TCT GAC C
GGT GTT TGA CGA AAG ACA TTG AGA CTG GA 3'--

Please replace the paragraph on page 35, beginning at line 13, with the following paragraph:

--In this method, the portable DNA sequences are those synthetic or naturally-occurring polynucleotides described above. In a preferred embodiment of the present method, the portable DNA sequence has the nucleotide sequence SEQ ID No: 5 as follows:--

Please replace the paragraph on page 39, beginning at line 18, with the following paragraph:

--In certain circumstances, the metalloproteinase inhibitor will assume its proper, active structure upon expression in the host microorganism and transport of the protein through the cell wall or membrane into the periplasmic space. This will generally occur if DNA coding for an appropriate leader sequence has been linked to the DNA coding for the recombinant protein. The preferred metalloproteinase inhibitors of the present invention will assume their mature, active form upon translocation out of the inner cell membrane. The structures of numerous signal peptides have been published, for example by Marion E.E. Watson in Nuc. Acid Res. 12: 5145-5164, 1984, specifically incorporated herein by reference. It is intended that these leader sequences, together

with portable DNA, will direct intracellular production of a fusion protein which will be transported through the cell membrane and will have the leader sequence portion cleaved upon release from the cell.--

Please replace the paragraph on page 41, line 10, with the following paragraph:

--Preparation of Poly(A⁺) RNA from HEF-SA Fibroblasts--.

Please replace the paragraph on page 56, beginning on line 10, with the following paragraph:

--The structure of FIBAC A is

(SEQ ID No: 10) GA TCC GCG ATC GGA GTG TAA GAA ATG TGC ACT
(SEQ ID No: 11) G CGC TAG CCT CAC ATT CTT TAC ACG TGA

 TGC GTT CCG CCG CAT CCG CAG ACT GCT TTC
 ACG CAA GGC GGC GTA GGC GTC TGA CGA AAG

 TGC AAC TCT GAC C
 ACG TTG AGA CTG GA--

Please replace the paragraph on page 56, beginning on line 19, with the following paragraph:

--Component oligonucleotide FA1 (SEQ ID No: 12) is:
GATCC GCGAT CGGAG TGTAA GAAAT GTGCA CTTGC--

Please replace the paragraph on page 56, beginning on line 21, with the following paragraph:

--Component oligonucleotide FA2 (SEQ ID No: 13) is:
GGAACG CAAGT GCACA TTTCT TACAC TCCGA TCGCG--

Please replace the paragraph on page 56, beginning on line 23, with the following paragraph:

--Component oligonucleotide FA3 (SEQ ID No: 14) is:
GTTC CGCCG CATCC GCAGA CTGCT TTCTG CAACT CTGAC C--

Please replace the paragraph on page 56, beginning on line 25, with the following paragraph:

--Component oligonucleotide FA4 (SEQ ID No: 15) is:
AGGTC AGAGT TGCAG AAAGC AGTCT GCGGA TGC GG C--

Please replace the sentence on page 57, line 4, with the following sentence:

--Linker A1 (SEQ ID No: 16) is: AATTGGCAG--

Please replace the sentence on page 57, line 5, with the following sentence:

--Linker A2 (SEQ ID No: 17) is: TCGACTGCC--

Please replace the first sentence on page 58 with the following sentence:

--The sequence of the sense strand (SEQ ID No: 18) is:--

Please replace the sentence on page 59, line 11, with the following sentence:

--Linker B1 (SEQ ID No: 19) is: GATCCCAGGCCTGCA--

Please replace the sentence on page 59, line 12, with the following sentence:

--Linker B2 (SEQ ID No: 20) is: GGCCTGG--

Please replace the sentence on page 68, line 4, with the following sentence:

--The second preferred sequence (SEQ ID No: 6) as set forth herein, i.e.,--

Please insert the enclosed paper copy of the sequence listing at the end of the specification.

IN THE CLAIMS:

Please delete claims 1-24 without prejudice or disclaimer thereof, and add new claims 25-42 as follows:

--25. (New) A purified collagenase inhibitor protein, said protein consisting essentially of an amino acid sequence selected from among the following:

- a) amino acid sequence SEQ ID NO: 1; or
- b) amino acid sequence SEQ ID NO: 2; or
- c) the amino acid sequences of a) or b), further having a Met at position -1;

or

- d) the amino acid sequence of a) or b), further having a leader sequence at the N-terminal, -1 position, wherein said leader sequence consists essentially of the following amino acid sequence from positions -38 to -1:

Gly His Arg Arg Arg Ser Ser Ala Gln Arg Asp Thr Arg Glu Pro Thr
Met Ala Pro Phe Asp Pro Trp Leu Leu His Pro Val Val Ala Val Ala
Asp Ser Pro Ser Arg Ala (SEQ ID NO: 3); or

- e) the amino acid sequence of a) or b) further having a leader sequence at the N-terminal, -1 position, wherein said leader sequence consists essentially of the following amino acid sequence from positions -22 to -1: Met Ala Pro Phe Asp Pro Trp
Leu Leu His Pro Val Val Ala Val Ala Asp Ser Pro Ser Arg Ala (SEQ ID NO: 4).

26. (New) The purified collagenase inhibitor protein of claim 25, wherein said protein comprises SEQ ID NO: 1, and wherein SEQ ID NO: 1 further comprises a glycine (Gly) at position 28, a threonine (Thr) at position 43, a glycine (Gly) at position 48, an alanine (Ala) at position 111, a glutamine (Glu) at position 125, and a threonine (Thr) at position 128, and optionally a methionine (Met) is at position -1.

27. (New) A recombinant plasmid or viral vector, wherein said recombinant plasmid or viral vector comprises DNA encoding a collagenase inhibitor protein, wherein said protein consists essentially of an amino acid sequence selected from among the following:

- a) amino acid sequence SEQ ID NO: 1; or
- b) amino acid sequence SEQ ID NO: 2; or
- c) the amino acid sequences of a) or b), further having a Met at position -1;

or

- d) the amino acid sequence of a) or b), further having a leader sequence at the N-terminal, -1 position, wherein said leader sequence consists essentially of the following amino acid sequence from positions -38 to -1:

Gly His Arg Arg Arg Ser Ser Ala Gln Arg Asp Thr Arg Glu Pro Thr
Met Ala Pro Phe Asp Pro Trp Leu Leu His Pro Val Val Ala Val Ala
Asp Ser Pro Ser Arg Ala (SEQ ID NO: 3); or

- e) the amino acid sequence of a) or b) further having a leader sequence at the N-terminal, -1 position, wherein said leader sequence consists essentially of the following amino acid sequence from positions -22 to -1: Met Ala Pro Phe Asp Pro Trp Leu Leu His Pro Val Val Ala Val Ala Asp Ser Pro Ser Arg Ala (SEQ ID NO: 4).

28. (New) A recombinant plasmid or viral vector, wherein said recombinant plasmid or viral vector comprises DNA encoding a collagenase inhibitor protein, wherein said protein comprises SEQ ID NO: 1, and wherein SEQ ID NO: 1 further comprises a glycine (Gly) at position 28, a threonine (Thr) at position 43, a glycine (Gly) at position 48, an alanine (Ala) at position 111, a glutamine (Glu) at position 125, and a threonine (Thr) at position 128, and optionally a methionine (Met) is at position -1.

29. (New) A eukaryotic or prokaryotic host cell transformed or transfected with the recombinant plasmid or viral vector of claim 27.

30. (New) A eukaryotic or prokaryotic host cell transformed or transfected with the recombinant plasmid or viral vector of claim 28.

31. (New) A process for producing a collagenase inhibitor protein, comprising:

- a) culturing the host cell of claim 29, under conditions wherein said host cell expresses said collagenase inhibitor; and
- b) collecting said expressed collagenase inhibitor.

32. (New) A process for producing a collagenase inhibitor protein, comprising:

- a) culturing the host cell of claim 30, under conditions wherein said host cell expresses said collagenase inhibitor; and
- b) collecting said expressed collagenase inhibitor.

33. (New) A recombinant-DNA method for microbial production of a collagenase inhibitor comprising:

- (a) culturing a host microorganism under conditions where said collagenase inhibitor is expressed, said host microorganism containing the vector pUC9-F5/237P10, said vector comprising a nucleotide sequence encoding a collagenase inhibitor;
- (b) culturing said host microorganism under conditions appropriate for expression of said collagenase inhibitor; and
- (c) harvesting said collagenase inhibitor.

34. (New) The method of claim 33, wherein said host microorganism is a bacterium.

35. (New) The method of claim 34, wherein said bacterium is a member of the genus *Bacillus*.
36. (New) The method of claim 35, wherein said bacterium is *Bacillus subtilis*.
37. (New) The method of claim 34, wherein said bacterium is *Escherichia coli*.
38. (New) The method of claim 34, wherein said bacterium is a member of the genus *Pseudomonas*.
39. (New) The method of claim 38, wherein said bacterium is *Pseudomonas aeruginosa*.
40. (New) The method of claim 33, wherein said host microorganism is a yeast.
41. (New) The method of claim 40, wherein said yeast is *Saccharomyces cerevisiae*.
42. (New) A host microorganism comprising the vector of claim 27 or 28.--

REMARKS

Applicants have amended the specification to correct errors of grammar and spelling, and/or to make amendments that were made in the parent, U.S. Application No. 09/452,817 (the '817 application). Specifically, Table 1, setting forth the amino acid sequence encoded by DNA from one embodiment of the portable DNA sequence, was added to the '817 application. Therefore, no new matter has been added by these changes.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005
202-408-4000

For the convenience of the Examiner, a marked-up copy of the amended paragraphs from the specification is attached as an Appendix. Nevertheless, the material as set forth above governs in case of any inconsistency.

New claims 25-42 are pending in the present application. Claims 25-42 are directed to purified collagenase inhibitor proteins, recombinant vector systems comprising DNA encoding a collagenase inhibitor protein, and recombinant DNA methods for making collagenase inhibitor proteins, as well as recombinant DNA methods for microbial production of collagenase inhibitors with vector pUC9-F5/237P10. These claims correspond directly to, or are derived from, earlier-filed claims in this series.

Specifically, claim 25 is drawn to the protein encoded by DNA sequences recited by allowed claim 25 in the '817 application. Claim 26 corresponds to claim 84 as filed in U.S. Application No. 08/474,553 on November 25, 1996. Claims 27 and 28, which recite plasmid or viral vectors that encode the collagenase inhibitor proteins of claims 25 and 26, and claim 42, which is drawn to a host microorganism comprising these vectors, are supported, for example by the claims as originally filed in U.S. Application No. 06/784,319 ("the '319 application"). Claim 33 and claims 35-41 which depend therefrom, which recite recombinant DNA methods for the microbial production of a collagenase inhibitor, wherein a host organism contains the vector pUC9-F5/237P10, find support, for example in claims 11-19 of the '319 application.

Although a Sequence Listing is not required in the instant application, Applicants have voluntarily complied with the Sequence Listing requirements by enclosing a paper copy of the Sequence Listing filed in parent U.S. Application No. 09/452,817, on

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005
202-408-4000

June 22, 2001. Applicants hereby request that the previously submitted computer readable copy of the Sequence Listing be associated with and used in the instant case.

The undersigned hereby states that the attached paper copy is identical to the computer readable copy of the Sequence Listing submitted on June 22, 2001, in the parent application, U.S. Patent Application Serial No. 09/452,817.

Applicants respectfully request the examination of this application and the timely notification of the allowability of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: November 14, 2001

By: 
William L. Strauss
Reg. No. 47,114

APPENDIX: Marked-up version

In the Specification:

The paragraph on page 4, beginning at line 4, has been amended as follows:

--Surprisingly, the present inventors have discovered a portable DNA sequence capable of directing the recombinant-DNA synthesis of metalloproteinase inhibitors. These metalloproteinase inhibitors are biologically equivalent to those isolated from human skin fibroblast cultures. The metalloproteinase inhibitors of the present invention, prepared by the recombinant DNA methods set forth herein, will enable increased research into prevention and treatment of metalloproteinase-induced connective tissue diseases. In addition, the metalloproteinase inhibitors of the present invention are useful in neutralizing [metalloproteinases] metalloproteinases, including the excess metalloproteinase associated with disease states. Therefore, it is believed that a cure for these diseases will be developed which will embody, as an active ingredient, the metalloproteinase inhibitors of the present invention. Furthermore, the metalloproteinase inhibitors of the present invention are capable of interacting with their metalloproteinase targets in a manner which allows the development of diagnostic tests for degradative connective tissue diseases using the newly discovered inhibitors.--

The paragraph on page 7, beginning at line 11, has been amended as follows:

--The coding strand of a first preferred DNA sequence which has been discovered has the following nucleotide sequence (SEQ ID No: 5):--

The paragraph on page 8, beginning at line 12, has been amended as follows:

--A second preferred DNA sequence has been discovered which has an additional nucleotide sequence 5' to the initiator sequence. This sequence, which contains as the eighty-second through four-hundred-thirty-second nucleotides nucleotides 1 through 351 of the first preferred sequence set forth above, has the following nucleotide sequence (SEQ ID No: 6):--

The paragraph on page 9, beginning at line 5, has been amended as follows:

--A third preferred DNA sequence which incorporates the 5' region of the second preferred sequence and the 3' sequence of the first preferred sequence, has the following nucleotide sequence (SEQ ID No: 7):--

The final paragraph on page 13 has been amended as follows:

--A first preferred portable DNA sequence of the present invention has a nucleotide sequence SEQ ID No: 5 as follows:--

The paragraph on page 15, beginning at line 6, has been amended as follows:

--A second preferred portable DNA sequence of the present invention has the following nucleotide sequence (SEQ ID No: 6):--

The final paragraph on page 15 has been amended as follows:

--In this second preferred sequence, an open reading frame exists from nucleotides 1 through 432. The first methionine of this reading frame is encoded by nucleotides [by] 49 through 51 and is the site of translation initiation. It should be noted that the amino acid sequence prescribed by nucleotides 49 through 114 is not found in the mature metalloproteinase. It is believed that this sequence is the leader peptide of the human protein.

The sentence on page 16, beginning at line 3, has been amended as follows:

--A third preferred portable DNA sequence has the [mucleotide] nucleotide sequence (SEQ ID No: 7):--

The nucleotide sequence on page 28, beginning on line 14, has been amended as follows:

HgIAI

--(SEQ ID No: 8) [5"] 5' GAT CCG TGC ACT TGT GTT CCA CCA CAC

(SEQ ID No: 9) GC ACG TGA ACA CAA GGT GGT GTG

 CCA CAA ACT GCT TTC TGT AAC TCT GAC C

 GGT GTT TGA CGA AAG ACA TTG AGA CTG GA 3'--

The paragraph on page 35, beginning at line 13, has been amended as follows:

--In this method, the portable DNA sequences are those synthetic or naturally-occurring polynucleotides described above. In a preferred embodiment of the present method, the portable DNA sequence has the nucleotide sequence SEQ ID No: 5 as follows:--

The paragraph on page 39, beginning at line 18, has been amended as follows:

--In certain circumstances, the metalloproteinase inhibitor will assume its proper, active structure upon expression in the host microorganism and transport of the protein through the cell wall or membrane into the periplasmic space. This will generally occur if DNA coding for an appropriate leader sequence has been linked to the DNA coding for the recombinant protein. The preferred metalloproteinase [metalloproteinase] inhibitors of the present invention will assume their mature, active form upon translocation out of the inner cell membrane. The structures of numerous signal peptides have been published, for example by Marion E.E. Watson in Nuc. Acid Res. [12: 515-5164] 12: 5145-5164, 1984, specifically incorporated herein by reference. It is intended that these leader sequences, together with portable DNA, will direct intracellular production of a fusion protein which will be transported through the cell membrane and will have the leader sequence portion cleaved upon release from the cell.--

The paragraph on page 41, line 10, has been amended as follows:

--Preparation of Poly(A⁺) [RNS] RNA from HEF-SA Fibroblasts--.

The paragraph on page 56, beginning on line 10, has been amended as follows:

--The structure of FIBAC A is

(SEQ ID No: 10) GA TCC GCG ATC GGA GTG TAA GAA ATG TGC ACT
(SEQ ID No: 11) G CGC TAG CCT CAC ATT CTT TAC ACG TGA

TGC GTT CCG CCG CAT CCG CAG ACT GCT TTC
ACG CAA GGC GGC GTA GGC GTC TGA CGA AAG

TGC AAC TCT GAC C
ACG TTG AGA CTG GA--

The paragraph on page 56, beginning on line 19, has been amended as follows:

--Component oligonucleotide FA1 (SEQ ID No: 12) is:
GATCC GCGAT CGGAG TGTAA GAAAT GTGCA CTTGC--

The paragraph on page 56, beginning on line 21, has been amended as follows:

--Component oligonucleotide FA2 (SEQ ID No: 13) is:
GGAACG CAACT GCACA TTTCT TACAC TCCGA TCGCG--

The paragraph on page 56, beginning on line 23 has been amended as follows:

--Component oligonucleotide FA3 (SEQ ID No: 14) is:
GTTC CGCCG CATCC GCAGA CTGCT TTCTG CAACT CTGAC C--

The paragraph on page 56, beginning on line 25, has been amended as follows:

--Component oligonucleotide FA4 (SEQ ID No: 15) is:
AGGTC AGAGT TGCAG AAAGC AGTCT GCGGA TGC GG C--

The sentence on page 57, line 4, has been amended as follows:

--Linker A1 (SEQ ID No: 16) is: AATTGGCAG--

The sentence on page 57, line 5, has been amended as follows:

--Linker A2 (SEQ ID No: 17) is: TCGACTGCC--

The first sentence on page 58 has been amended as follows:

--The sequence of the sense strand (SEQ ID No: 18) is:--

The sentence on page 59, line 11, has been amended as follows:

--Linker B1 (SEQ ID No: 19) is: GATCCCAGGCCTGCA--

The sentence on page 59, line 12, has been amended as follows:

--Linker B2 (SEQ ID No: 20) is: GGCCTGG--

The sentence on page 68, line 4, has been amended as follows:

--The second preferred sequence (SEQ ID No: 6) as set forth herein, i.e.,--

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005
202-408-4000